

contacting said array of extraction probes with sample aliquots suspected of comprising at least one of said analytes; and separating said array of extraction probes from said sample aliquots.

60. The method of claim 59 wherein each extraction probe comprises a different extraction phase.

61. The method of claim 59 wherein each sample aliquot is different.

62. The method of claim 59 wherein each fiber has a diameter of less than 100 microns.

63. The method of claim 62 wherein each fiber has a diameter of less than 1 micron.



REMARKS:

General

Additional claims have been added in the application. Additional claims fees of \$567, calculated as shown on the Patent Application Fee Determination Record filed herewith, are enclosed.

Claim Rejections – 35 USC §102

Claims 1-8 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,279,742 to Markell, et al.

Independent claim 1 has been amended to provide that the extraction probes are freestanding particles. Freestanding particles are described, for example, on page 25, lines 5-10 and page 11, lines 29-30 of the present application. Dependent claim 6 has been rewritten in independent form, incorporating the limitations of original claim 1. Claims 2-5 and 7-8 have been amended to depend from amended claim 6.

Amended claims 1 and 6 recite a method for extracting a plurality of analytes from a sample using extraction probes comprising a solid support and an extraction phase. In amended claim 1 the solid support is a freestanding particle, and in amended claim 6, the extraction phase is combinatorially derived. In rejecting claims 1-8 as being anticipated by the Markell, et al. patent, the Examiner made no mention of combinatorially-derived extraction phases being disclosed or suggested in the reference. Markell, et al. neither teaches nor suggests either of these two features.

Markell, et al. is directed to a method for isolating contaminants from a fluid sample by flowing the sample through a solid phase extraction medium. The extraction medium is a composite structure (a sheet or disk) in which sorbent particles are enmeshed in a fibril matrix of polytetrafluoroethylene (PTFE).

Regarding amended claim 1, freestanding particles are not disclosed or suggested in Markell, et al. The component particles of the composite structure are not freestanding. Not only are they contained within bounds of the disk, the particles are physically immobilized within the disk's fiber matrix. As Markell, et al. states, "[i]n such a structure almost all of the particles are separate one from another and each is isolated in a cage that restrains the particle on all sides by a fibrillated mesh of PTFE microfibers" (col. 8, lines 62-66; emphasis added).

By contrast, the freestanding particles of the present invention are "freely dispensable in a liquid and not permanently associated with a stationary phase" (see page 25, lines 5-12). Accordingly, the particles "may be introduced into the sample where they can independently assort in three-dimensions," allowing the extraction phase associated with each particle to contact and interact with analytes present in the sample (page 10, lines 4-7). The use of such freestanding particles provides advantages over extraction probes arranged in a planar configuration, such as in an array or disk. For example, the extraction may be performed in smaller volumes of sample (see page 11, line 29 - page 12, line 3), and because the extraction phase and the sample are both mobile, equilibration time is shortened as "encounters between [the extraction phase and the sample] occur more frequently and the capture of analyte molecules is more rapid" (page 32, lines 14-17).

There would be no motivation to free the sorbent particles of Markell, et al. from their “PTFE cages,” because it is properties of the PTFE-particulate composite structure that are responsible for the purported advantages such as strength, self-support, uniform porosity and void volume, uniform distribution of particulate, and convenience (see, e.g., col. 8, lines 21-26 and lines 57-62). Indeed, Markell, et al. states that “particles in the PTFE fibrillated matrix provide superior separatory capabilities” over particles not in the matrix (col. 3, lines 55-65). In addition, Markell, et al. states that it is advantageous to “stack” disks that contain different particulates so as to have different selectivities for different contaminants. By separately eluting the disks and by using alternate stacking orders, additional information about the types of compounds in each eluting fraction can be obtained (col. 14, lines 29-36; Example 2). These advantages are possible only because the different particles are embedded components of a specific disk that can be separately manipulated and identified. Freeing the particles from their PTFE cages would eliminate these advantages because the particles could not be separately manipulated or identified. Significantly, Markell, et al. does not disclose or suggest a means to manipulate (e.g., recover the particles from solution or prevent them from being swept away with the sample flow) or to identify particles other than by their physical association with the disk in which they are embedded. In fact, as noted above, Markell, et al. actually teaches away from using particles not enmeshed in a PTFE matrix. The applicant therefore submits that amended claim 1 is patentable over Markell, et al.

Regarding claim 6, combinatorially-derived extraction phases are neither disclosed nor suggested in Markell, et al. Although Markell, et al. states that various coatings can be used with the particulates to provide selectivity in molecular separation, there is no disclosure of combinatorially-derived extraction phases.

As described on page 37, lines 14-26 of the present application, combinatorial methods provide a diverse range of extraction phases, increasing the likelihood that any given analyte will be extracted from a biological sample. In addition, use of combinatorial-derived extraction phases is most efficient only when a large number of differentiable extraction probes is possible, each having a different extraction phase. In

this way, a set of such probes can be used to fractionate a sample and provide a complete description (or “fingerprint”) of its components, including known and unknown species.

In contrast, the extraction medium of Markell, et al. is designed for removing known hazardous organic contaminants (e.g., pesticides) from fluids, not for fingerprinting the contents of a sample. Indeed, Markell, et al. instructs on how to select the proper coating to remove the suspected contaminants, see col. 10, lines 46-48 (“one or more types of particulate [are] chosen, each having optimum extraction efficiency for individual contaminants”), or the known component of interest for later elution (col. 9, lines 26-29) and states that many such coatings are commercially available (col. 4, lines 63-64). Indeed, exposing a sample to a large number of combinatorially derived surfaces would not be an effective way to remove a contaminant (the stated aim of Markell, et al.). Moreover, there is no indication that the stacked-disk format of Markell, et al. would be able to accommodate a sufficiently large number of separately identifiable extraction probes. Markell, et al. mentions using a small number of different sheets or discs. For example, FIG. 2 shows a stack of five disks, each of which can contain a different type of particulate; Example 2 describes a system using 2 disks; and Example 4 describes a system using 3 disks. The few disks that Markell, et al. discloses can be stacked to extract multiple contaminants would be insufficient to accommodate combinatorially-derived extraction phase. If this method disclosed in Markell, et al. were to be used to extract a sample with combinatorially derived surfaces, many more discs would be needed, which would require prohibitively thicker stacks through which to flow the sample, or a prohibitively large number of serial inquiries. Moreover, the same result as the present invention would not be obtained using the disks of Markell, et al. Because the sample would encounter the disks one after the other, each disk being exposed to a sample with a different set of components than the disk before (i.e., the sample would lack components extracted by earlier disks). For these reasons, one of skill in the art would not be motivated to use combinatorially-derived extraction phases in the method of Markell, et al. Thus, applicant submits that amended claim 6 and its dependent claims 2-5 and 7-8 are patentable over Markell, et al.

New dependent claims 15-28 depend from amended claim 1, and new dependent claims 29-43 depend from amended claim 6. These claims are asserted to be patentable over Markell, et al. for at least the reasons stated above. Support for these new claims is found, for example, as follows: claim 15: page 24, lines 28-30; claim 16: page, 35, lines 10-12; claim 17: page 26, lines 23-24; claim 18: page 26, lines 25-27; claim 19: page 26, lines 27-30; claims 20-22: page 11, lines 22-24; claim 23: page 38, lines 13-18, and page 34, lines 22-24; claim 24: page 34, table, and page 38, lines 17-18; claims 25-27: page 24, line 31, through page 25, line 1; claim 28: page 8, lines 25-28; claim 29: page 37, lines 22-24; claims 30-31: page 38, lines 10-12; claim 32: page 38, lines 13-14; claim 33: page 39: lines 23-24; claim 34: page 10, lines 25-27, and page 38, lines 14-18; claim 35: page 10, lines 27-29; claim 36: page 11, lines 1-5, and page 14, lines 12-14; claims 37-40: page 11, lines 22-24, and page 8, lines 25-28; claims 41-42: page 37, lines 1-2; and claim 43: page 8, lines 25-28.

Claim Rejections – 35 USC §103

Claims 9-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Markell, et al. in view of Michael, et al., “Randomly Ordered Addressable High-Density Optical Sensor Arrays,” Anal. Chem. 70:1242-1248 (1998).

Claim 9, which recites a method for simultaneously conducting a plurality of assays to a plurality of analytes using encoded extraction probes, has been amended to recite that the solid support of the extraction probe is a freestanding particle. Neither Markell, et al. nor Michael, et al. disclose or suggest contacting freestanding particles with a sample. Like the “PTFE caged” particulates in Markell, et al. (discussed above), the microbeads in Micheal, et al. are not freestanding – they are immobilized in a planar array.

Before being contacted with the sample, the encoded beads of Michael, et al. are immobilized on the surface by random distribution into wells of a chemically etched optical imaging fiber (see, e.g., Michael, et al., FIG. 3). In the series of experiments disclosed in Michael, et al., the sensor array was exposed to six different solutions and “neither loss nor rearrangement of the microspheres was observed” (page 1247, first full paragraph). Indeed, Michael, et al. states that the microwell “entraps” the microspheres

(see page 1247, first full paragraph). Michael, et al. does not disclose or suggest a means for ejecting the particles from the sensor surface, and it is clear that a particle must be immobilized on the array to be read. A *prima facie* case of obviousness therefore cannot be established, and applicant submits that amended claim 9 is patentable over the prior art of record.

Claim 10 recites a method for extracting analytes using an array of extraction probes contacted with an array of capillaries containing sample aliquots. The extraction probes are positioned within the capillaries and then removed, thereby extracting the analytes from the sample aliquots. Because the extraction probes are position addressable, it is unnecessary to encode them for identification purposes.

The Examiner asserts that, in view of Michael, et al., it would have been obvious to encode the microparticles of Markell, et al. and arrange them in ordered addressable arrays to allow for more efficient isolation and sensing of target analytes. However, arranging the particulates of Markell, et al. in an array does not yield the claimed invention. Neither Markell, et al. or Michael, et al. teaches or suggests a position-addressable array. Nor does either reference teach or suggest an array of capillaries containing sample aliquots.

While Michael, et al. discloses “randomly ordered addressable high-density optical arrays,” these are not position-addressable arrays. In the arrays of Michael, et al., fluorescence-encoded particles with different reactive chemistries are randomly distributed into the wells of an array of micrometer-scale wells. The identities of the reactive chemistries are not determined by the positions of the beads in the arrays, but rather by the fluorescence of the microspheres; see Michael, et al., page 1247, first full paragraph (“[A] key feature of this technology is that the identity of each microsphere is not determined by its position in the array, but by its encoded signature.”). According to Michael, et al., position-addressable arrays have a number of drawbacks, including expensive and complicated fabrication as well as lack of flexibility in specifying capture chemistries. The purpose of the method of Michael, et al. is to provide a solution to these problems associated with position-addressable arrays (see Michael, et al., abstract)

Thus Michael, et al.⁴ would provide no motivation to arrange the particles of Markell, et al. in position-addressable arrays, as Michael, et al. actually teaches away from such arrays. Additionally, position-addressable arrays would not be helpful in achieving the purpose of the Markell, et al. device: The efficient removal of contaminants from liquid samples. Position-addressable arrays provide for extraction of the same analytes from multiple samples or extraction of multiple different analytes from the same sample. In all cases, it is important to identify both the analyte and sample corresponding to a particular array location. In the case of Markell, et al., however, there is no need for (nor, as pointed out above, would it accommodate) significant multiplexing or identification and quantification of analytes. Thus, it would not be beneficial to assemble the particles into position-addressable arrays.

Likewise, there would be no motivation to use an array of capillaries to introduce fluid to the method of Markell, et al., which is designed to extract contaminants as fluid flows through the disks.

Moreover, as the applicant explained above, the particulates used in Markell, et al. are integral components of a composite structure, and there is no disclosure or suggestion to separate the particles from the composite structure. There would be no advantage to encoding the particulates contained in the composite structure or remove them from the composite structure and one of skill in the art would not be motivated to do so.

Thus not only does the combination of references not teach or suggest all of the claim elements, but there would be no motivation to introduce these elements into the methods disclosed in Markell, et al. or Michael, et al. A *prima facie* case of obviousness cannot be established, and the applicant submits that claim 10 is patentable over Markell, et al. and Michael, et al. Claim 11 depends from claim 10 and is therefore submitted to be patentable for at least the same reasons set forth above. Minor formal amendments have been made to claim 10.

Claim 12 has been amended to recite that the plurality of extraction probes contains at least two hundred differentiable extraction probes. Support for this amendment is found, for example, on page 24, line 28, through page 25, line 1 of the

present application. Neither Markell, et al. nor Michael, et al. discloses at least 200 differentiable particles. Michael, et al. discloses only three differentiable particles. Michael, et al. speculates that, with undisclosed “improvements in the encoding procedure and the exploration of new dye pairs,” it may be possible to have as many as 150 differentiable particles (Michael, et al.; page 1246, first paragraph). However, to do so would involve distinguishing 10 ratios of 15 binary combinations of 6 different dyes. Because of the high spectral overlap of fluorescent dyes, it is questionable whether such a goal can be achieved.

Markell, et al. mentions using a small number of different sheets or discs, as discussed above, but none approaching the 200 differentiable particles of claim 12. There is no indication that as many as 200 particle types would be needed or even desirable in the device of Markell, et al. Since the purpose of the device of Markell, et al. is not to profile a fluid, but rather to remove only unwanted contaminants, it is unlikely that there would be a need for as many as 200 different particle types. The applicant therefore submits that amended claim 12 and its dependent claims 13 and 14 are patentable over Markell, et al. and Michael, et al.

In addition, new dependent claims 44-52 depend from amended claim 12. These claims are asserted to be patentable over Markell, et al. and Michael, et al. for at least the reasons stated above. Support for these new claims is found, for example, as follows: claim 44: page 20, line 13, through page 21, line 6; claim 45: page 28, lines 15-21; claim 46: page 36, lines 30-37; claim 47: page 10, lines 23-24; claim 48: page 16, lines 15-17; claim 49: page 16, lines 15-18, page 34, lines 22-24, and page 38, lines 13-18; claim 50: page 10, lines 25-27, and page 38, lines 14-18; claim 51: page 19, lines 17-19; and claim 52: page 39, lines 23-26.

New independent claim 53 and its dependent claims 54-58 and new independent claim 59 and its dependent claims 60-63 have also been added. Independent claim 53 is similar to claim 1, but specifies that at least 200 differentiable extraction phases are used, and that the extraction probes are distinguished. Support for this addition material is found, for example, on page 24, line 28, through page 25, line 4. As explained above, neither Markell, et al. nor Michael, et al. teaches or suggests the use of at least 200

differentiable extraction probes, and the applicant therefore submit that claim 53 and its dependent claims 54-58 are patentable over the prior art of record.

Independent claim 59 is similar to claim 10, but specifies that the solid phases are fibers arranged in a position-addressable array. As set forth above, neither reference teaches or suggests position-addressable arrays. The application therefore submits that claim 59 and its dependent claims 60-63 are patentable over the prior art of record.

Thus, the applicant request that the Examiner reconsider the application and issue a Notice of Allowance in the next Office Action.

Respectfully submitted,

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MARKED UP VERSION OF THE SPECIFICATION AMENDMENTS:

Page 1, Lines 8-17:

This application claims the benefit of United States Provisional Application Serial No. 60/189,151, filed March 14, 2000, entitled “Nanoscale Barcodes”; United States Provisional Application Serial No. 60/190,247, filed March 17, 2000, entitled “Colloidal Rod Particles as Barcodes”; United States Provisional Application Serial No. 60/194,616, filed April 5, 2000, entitled[,] “Nanobarcodes: Technology Platform for Phenotyping”:[,] United States Provisional Application No. 60/222,214, filed August 1, 2000, entitled “Combinatorial Separation of Biological Material”; United States Provisional Application Serial No. 60/238,181 [_____], filed October 5, 2000, entitled[,] “Methods for Solid Phase Nanoextraction and Desorption”; and United States Provisional Application Serial No. 60/239,662 [_____], filed October 12, 2000, entitled “Methods for Solid Phase Nanoextraction and Desorption.”[.]

MARKED UP VERSION OF AMENDED CLAIMS:

1. (amended) A method for extracting a plurality of analytes from a sample, comprising the steps of:
providing a plurality of extraction probes capable of adsorbing [an analyte] analytes,
wherein [said] each extraction [probes are] probe [comprised of] comprises a
[solid support] freestanding particle and an extraction phase;
contacting said extraction [probe] probes with a sample suspected of comprising at
least one of the analytes; and
[separation of] separating said extraction [probe] probes from the sample.
2. (amended) The method of claim [1] 6, wherein said solid support [is a
microparticle] comprises a nanoparticle.

3. (amended) The method of claim 2 wherein said [microparticle] nanoparticle comprises [is] a nanobarcode.
4. (amended) The method of claim [1] 6, wherein said solid support comprises [is] a bead.
5. (amended) The method of claim [1] 6, wherein said solid support [is] comprises a fiber.
6. (amended) A [The] method [of claim 1, wherein said extraction phase is] for extracting a plurality of analytes from a sample, comprising the steps of: providing a plurality of extraction probes capable of adsorbing analytes, wherein each extraction probe comprises a solid support and a combinatorially-derived extraction phase; contacting said extraction probes with a sample suspected of comprising at least one of the analytes; and separating said extraction probes from the sample.
7. (amended) The method of claim [1] 6, wherein said extraction phase [is] comprises a polymer.
8. (amended) The method of claim [1] 6, further comprising the step of detecting for at least one analyte extracted from said sample.
9. (amended) A method for simultaneously conducting a plurality of assays to a plurality of analytes comprising:
contacting a solution that may contain the analytes with a plurality of extraction probes, wherein each extraction probe comprises a [solid support] freestanding particle and an extraction phase, and wherein the nature of each extraction phase is encoded by [the solid support] a freestanding particle to which it is associated; and

detecting for the presence of at least one analyte associated with said extraction probes.

10. (amended) A method for extracting a plurality of analytes from a sample, comprising the steps of:
providing a position-addressable array of extraction probes, [such probes] each probe [comprised of] comprising a solid support and an extraction phase;
providing an array of capillaries addressable by the array of extraction probes, the capillaries containing aliquots [alliquots] of the sample;
contacting the array of extraction probes with the array of capillary tubes such that the extraction probes are positioned within the capillary tubes;
separating the array of extraction probes from the array of capillaries, such as that the extraction probes are separated from the sample.
11. The method of claim 10 wherein each capillary tube comprises a different sample.
12. (amended) An assembly comprising at least 100 differentiable [A plurality of] extraction probes, [comprised of] each extraction probe comprising a solid support and an extraction phase, wherein said extraction probes comprise [of] a plurality of different types of extraction phases.
13. (amended) The [plurality] assembly of extraction probes of claim 12 wherein the nature of the extraction [phase is] phases are encoded by the solid [support] supports.
14. (amended) The [plurality] assembly of extraction probes of claim [13] 12 wherein the solid support is a [microparticle] nanoparticle.

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